

Onset of action of indacaterol in patients with COPD: Comparison with salbutamol and salmeterol-fluticasone

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Background: Indacaterol is a novel, inhaled once-daily ultra-long-acting β_2 -agonist for the treatment of chronic obstructive pulmonary disease (COPD).

Objectives: This study compared the onset of action of single doses of indacaterol 150 and 300 μg with salbutamol 200 μg , salmeterol-fluticasone 50/500 μg , and placebo in moderate-to-severe COPD patients.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled crossover study. The primary variable was forced expiratory volume in one second (FEV_1) at five minutes postdose.

Results: Out of 89 patients randomized (mean age 62 years), 86 completed the study. At five minutes postdose, both indacaterol doses were statistically and clinically superior to placebo ($P < 0.001$), with treatment–placebo differences in FEV_1 of 100 (95% confidence interval [CI] 70–130) mL and 120 (95% CI 90–150) mL for indacaterol 150 and 300 μg , respectively. FEV_1 at five minutes postdose with both indacaterol doses was numerically higher than for salbutamol (10 and 30 mL for indacaterol 150 and 300 μg , respectively) and significantly higher than for salmeterol-fluticasone (50 mL, $P = 0.003$; 70 mL, $P < 0.001$, respectively). Moreover, both indacaterol doses showed significantly higher FEV_1 than placebo ($P < 0.001$) at all postdose time points. The numbers of patients with an FEV_1 increase of at least 12% and 200 mL at five minutes postdose were 16 (18.8%), 24 (27.6%), 20 (23.3%), 8 (9.1%), and 3 (3.4%) for indacaterol 150 and 300 μg , salbutamol 200 μg , salmeterol-fluticasone 50/500 μg , and placebo, respectively.

Conclusions: Single doses of indacaterol 150 and 300 μg demonstrated a fast onset of action similar to that for salbutamol and faster than that for salmeterol-fluticasone.

Keywords: indacaterol, onset of action, chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD), being a condition associated with increased morbidity and mortality, causes a substantial and increasing burden to society in many countries.^{1,2} The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline³ recommends regular use of bronchodilators for symptomatic management of COPD, including inhaled β_2 -agonists and anticholinergics.³ As with all chronic diseases, nonadherence to treatment is common in patients with COPD, potentially leading to adverse health outcomes and reduced quality of life.⁴ Characteristics of COPD medications and regimens may often contribute to nonadherence, and therefore should be considered when selecting the appropriate treatment for a patient. In general, more complex regimens result in suboptimal adherence,⁵ with frequency of dosing regarded as one of the principal factors that negatively affect adherence.⁶

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In addition, adherence is lower for medications that do not have an immediate effect on symptoms.⁷

Indacaterol is a novel, inhaled once-daily ultra-long-acting β_2 -agonist (LABA)⁸ for the treatment of COPD. In preclinical studies, the onset of action of indacaterol was similar to that of salbutamol and of formoterol, and was significantly faster than that of salmeterol.⁹ In previous clinical studies, indacaterol has demonstrated 24-hour bronchodilation on once-daily dosing, along with a good overall safety and tolerability profile.^{10–12} The present study was conducted to evaluate the onset of action of single doses of indacaterol 150 and 300 μg in comparison with that of salbutamol 200 μg (the standard “fast-onset” bronchodilator), the combination of salmeterol 50 μg and fluticasone 500 μg (salmeterol-fluticasone 50/500 μg), and placebo in patients with moderate-to-severe COPD.

Methods

This was an international, multicenter, randomized, double-blind, placebo-controlled, crossover, single-dose study. Institutional review board or independent ethics committee approval was obtained from each participating study center. The study was conducted in accordance with the Declaration of Helsinki (1989) and local applicable laws and regulations. All patients provided written informed consent prior to participation in the study.

Study population

Patients of either gender, aged ≥ 40 years, with moderate-to-severe COPD (according to the GOLD 2005 guideline), smoking history of ≥ 20 pack years, postbronchodilator forced expiratory volume in one second (FEV_1) $\geq 30\%$ but $< 80\%$ of the predicted normal value, and postbronchodilator $\text{FEV}_1/\text{forced vital capacity (FVC)} < 70\%$ were eligible for enrolment in the study.

Patients were excluded from the study if they had any concomitant pulmonary disease, type I diabetes or uncontrolled type II diabetes, uncontrolled hypertension, unstable ischemic heart disease, or malignancy. Patients who had a history of asthma, had been hospitalized for a COPD exacerbation within six weeks prior to screening or during the run-in period, or had experienced respiratory tract infection within six weeks prior to screening, were also excluded.

The following medications were prohibited at any time during the study (the minimum washout period is shown in brackets): long-acting anticholinergics (seven days), short-acting anticholinergics (eight hours), fixed-dose combination of a β_2 -agonist and an inhaled corticosteroid

(ICS, 48 hours), fixed-dose combination of a short-acting β_2 -agonist and a short-acting anticholinergic (eight hours), other LABAs (48 hours), short-acting β_2 -agonists (other than those prescribed in the study, six hours), xanthine derivatives (one week), and parenteral or oral corticosteroids (one month). Patients on fixed-dose combinations of a β_2 -agonist and an ICS were to be switched to the equivalent ICS prior to the run-in period, with the dose and dosage regimen to remain unchanged for the duration of the study. Patients on ICS at the screening visit were to continue ICS for the duration of the study, again at a dose and regimen to remain unchanged.

Study design and treatments

The study comprised a prescreening visit, a 14-day screening/run-in period, and five single-dose treatment periods. During the prescreening visit, patients' ongoing COPD medications were reviewed and, if necessary, any prohibited medication was adjusted to an allowable COPD therapy. After the screening visit, patients entered into a 14-day run-in period, during which their eligibility was assessed. At baseline, patients were randomized equally (using a validated automated system) to one of five treatment sequences to receive indacaterol 150 μg and 300 μg delivered via a single-dose dry powder inhaler, salbutamol 200 μg via the manufacturer's proprietary multidose dry powder inhaler, salmeterol-fluticasone 50/500 μg fixed-dose combination via the manufacturer's proprietary multidose dry powder inhaler, and placebo. Each treatment sequence comprised five double-blind, single-dose treatment periods, with treatment periods separated by a 4- to 7-day washout period. At 4–7 days after the last treatment visit, patients were contacted by telephone for a study completion call.

Patients inhaled through three different devices on each visit (one inhalation from a single-dose dry powder inhaler and one from each of the two multidose dry powder inhalers used in the study), with the order of devices randomly assigned at the start of the study. Treatment allocation was concealed from the patients, investigating staff, and the clinical trial team by the use of matching placebo inhalers all identical in packaging, labeling, and schedule of administration. An unblinded pharmacist (or designee) prepared the individual patient-specific packs from supplied bulk medication. Salbutamol was the only rescue medication permitted throughout the study, although visits had to be rescheduled if salbutamol was taken within six hours prior to the start of the visit.

Assessments and outcomes

Efficacy

All efficacy evaluations were based on spirometric assessment of lung function, performed at 50 and 15 minutes predose and at 5, 15, and 30 minutes, and at 1 and 2 hours postdose. The postdose time was measured from the time the first device was used at each study visit (the three devices were used in a randomized order, as described above). All spirometry equipment and spirometric testing were in accordance with the American Thoracic Society/European Respiratory Society standards.¹³

The primary efficacy variable was FEV₁ at five minutes postdose. The primary objective was to compare indacaterol 150 and 300 µg and placebo in terms of FEV₁ at five minutes postdose. The secondary objectives were to compare indacaterol 150 and 300 µg with salbutamol 200 µg and salmeterol-fluticasone 50/500 µg, and to compare salmeterol-fluticasone 50/500 µg with salbutamol 200 µg in terms of FEV₁ at five minutes postdose. The other efficacy variables were FEV₁ at other scheduled time points; the proportion of patients with at least 10%, 12%, and 15% increase in FEV₁ from baseline to each scheduled time point; and the proportion of patients with at least a 12% and 200 mL increase in FEV₁ from baseline to each scheduled time point.

Safety

Safety assessments included recording of adverse events and serious adverse events, along with evaluation of their severity, duration, and relationship to study drug. In addition, samples were collected for hematology and blood chemistry (including serum potassium and blood glucose), and vital signs and electrocardiogram assessments were recorded.

Sample size calculation and statistical analysis

It was estimated that 53 patients were needed to complete the study, assuming a difference of 120 mL between each indacaterol dose and placebo in terms of FEV₁ at five minutes postdose, a standard deviation of 240 mL, a two-sided significance level of 5% (adjusted to 2.5% using a Bonferroni correction for the two main treatment comparisons, that is, indacaterol [150 and 300 µg] versus placebo), and a power of 90%. As there were five treatment sequences and six inhaler orders for individual treatment sequences, a total of 60 patients with evaluable measurements were required in order to have an equal number of patients per inhaler order and per treatment sequence. Allowing for a 15% dropout rate and with the number inflated to ensure balance across

the treatment sequences, it was calculated that 75 patients needed to be randomized.

The primary efficacy analysis was performed on a modified intent-to-treat population that included all randomized patients who received at least one dose of study drug (the modification was that patients were analyzed according to treatment received in each treatment period). The safety population, which was used in the analysis of all safety variables, included all patients who received at least one dose of study drug.

The primary efficacy variable, FEV₁ at five minutes postdose, was analyzed using a mixed model, with treatment group and period modeled as fixed effects, patient as a random effect, and period baseline FEV₁ as a covariate. Period baseline FEV₁ was defined as the average of the FEV₁ values measured 50 and 15 minutes prior to study drug administration in each treatment period. For the primary variable, estimated least squares means and treatment differences with associated 95% confidence intervals (CIs) are presented. A multiplicity adjustment for the two main treatment comparisons in the study was made using a step-down Dunnett's test implemented in a closed test procedure. Similar mixed-effect models were used to analyze FEV₁ at the other time points.

The proportion of patients with at least a 10%, 12%, and 15% increase in FEV₁ from baseline at each scheduled time point, and the proportion of patients with at least a 12% and 200 mL increase in FEV₁ from baseline at each scheduled time point, were summarized using descriptive statistics and analyzed by logistic regression for each time point. The logistic regression model included terms for period, treatment, and period baseline as fixed effects and patient as a random effect. The estimated odds ratios are presented along with the associated 95% CIs and *P* values. All analyses were performed using SAS statistical software (version 9.1.3 for Windows; SAS Institute Inc., Cary, NC).

Results

Patient disposition, demographics, and baseline characteristics

Of 114 patients screened, 89 were eligible to participate in the study. All eligible patients were randomized to treatment sequences, and no patient received the study drug in error; thus, the safety population was identical to the modified intent-to-treat population. Eighty-six (96.6%) patients completed the study, while three (3.4%) patients discontinued from the study (one each due to withdrawal of consent, loss to follow-up, and protocol deviation).

Demographic and baseline clinical characteristics are summarized in Table 1. More than half of the patients (61.8%) were aged <65 years, the majority was Caucasian, and more than half were male. All patients were current or former smokers.

Table 1 Demographic summary and baseline clinical characteristics (safety population)

Variable	Total, n = 89
Age (years)	
Mean \pm SD	62.3 \pm 8.37
Range	43–79
Sex, n (%)	
Male	54 (60.7)
Female	35 (39.3)
Race, n (%)	
Caucasian	88 (98.9)
Black	1 (1.1)
Weight (kg)	
Mean \pm SD	80.1 \pm 17.27
Range	49.0–120.0
Duration of COPD (years)	
Mean \pm SD	6.8 \pm 5.81
Range	0.1–27.0
ICS use, n (%)	
Yes	49 (55.1)
No	40 (44.9)
COPD medication discontinued prior to start of study treatment, n (%)	
Long-acting anticholinergic	31 (34.8)
β_2 -agonist plus steroid	28 (31.5)
Long-acting β_2 -agonist	23 (25.8)
β_2 -agonist plus anticholinergic	14 (15.7)
Xanthine	9 (10.1)
Short-acting anticholinergic	4 (4.5)
Smoking history, n (%)	
Exsmoker	40 (44.9)
Smoker	49 (55.1)
Postbronchodilator FEV ₁ (L) at screening	
Mean \pm SD	1.48 \pm 0.420
Range	0.77–2.60
Postbronchodilator FVC (L) at screening	
Mean \pm SD	2.94 \pm 0.851
Range	1.21–5.24
Postbronchodilator FEV ₁ (% predicted) at screening	
Mean \pm SD	53.5 \pm 12.73
Range	31.6–83.8
Postbronchodilator FEV ₁ /FVC at screening (%)	
Mean \pm SD	51.4 \pm 9.08
Range	27.4–68.8
FEV ₁ reversibility (% increase) at screening	
Mean \pm SD	9.1 \pm 12.22
Median	6.1
25 th –75 th quartile	0.9–16.5
Range	–22.8 – 41.0

Note: FEV₁ reversibility at screening was measured 15–30 minutes after inhalation of 400 μ g salbutamol.

Abbreviations: SD, standard deviation; ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease.

Efficacy

For the primary efficacy variable (FEV₁ at five minutes postdose), the least squares mean values for indacaterol 150 and 300 μ g were higher than that for placebo by 100 and 120 mL, respectively ($P < 0.001$, Figures 1 and 2). Both indacaterol doses showed a numerically higher FEV₁ at five minutes postdose than salbutamol (differences of 10 and 30 mL for indacaterol 150 and 300 μ g, respectively, versus salbutamol, Figure 2). Moreover, both indacaterol doses produced significantly higher FEV₁ at five minutes postdose than salmeterol-fluticasone (50 mL, $P = 0.003$ and 70 mL, $P < 0.001$, Figure 2).

Serial measurements of FEV₁ at all postdose time points are shown in Figure 3. Both indacaterol doses showed significantly higher FEV₁ than placebo ($P < 0.001$) at all postdose time points, significantly higher than salmeterol-fluticasone ($P < 0.05$) at five and 15 minutes postdose, and numerically (150 μ g) or statistically (300 μ g) higher than salmeterol-fluticasone at 30 minutes postdose (Figure 4). The difference between indacaterol 300 μ g and salbutamol was statistically significant at two hours postdose ($P < 0.001$).

The proportion of patients with at least a 10%, 12%, or 15% increase in FEV₁ from baseline at five minutes postdose was higher in both indacaterol groups compared with salmeterol-fluticasone ($P < 0.01$), and similar to salbutamol (Table 2). At 30 minutes postdose, the proportion of patients with at least a 10%, 12%, or 15% increase in FEV₁ was higher in both indacaterol groups compared with placebo, with the proportions in the indacaterol 300 μ g group higher than those in the salmeterol-fluticasone group (Table 3). The proportion was also higher in both indacaterol groups than placebo at five and 15 minutes, and at one and two hours postdose ($P < 0.001$ for all). The proportions of patients with at least a 12% and 200 mL increase in FEV₁ from baseline at five minutes postdose in the indacaterol 150 μ g, indacaterol 300 μ g, and salbutamol 200 μ g groups were higher than that in the salmeterol-fluticasone 50/500 μ g and placebo groups ($P < 0.05$ for all, Figure 5).

Safety

Overall, adverse events were reported in 3/86 (3.5%), 3/87 (3.4%), 4/86 (4.7%), 6/88 (6.8%), and 4/87 (4.6%) patients taking indacaterol 150 μ g, indacaterol 300 μ g, salbutamol 200 μ g, salmeterol-fluticasone 50/500 μ g, and placebo, respectively. All reported adverse events were mild or moderate in severity, and none were suspected of being related to study drug. There were no deaths or serious adverse events

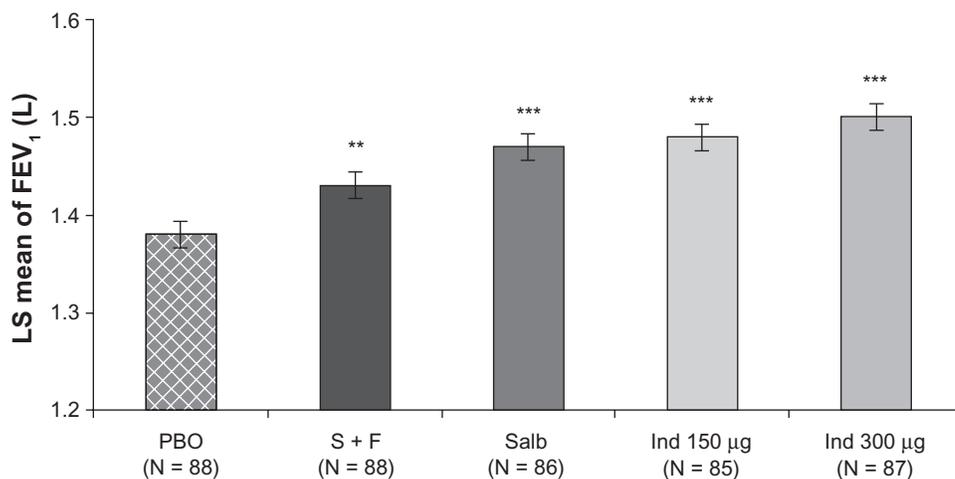


Figure 1 Least squares mean FEV₁ ± standard error of the mean at five minutes postdose.

Note: Differences versus placebo significant at ***P* < 0.01 and ****P* < 0.001.

Abbreviations: Ind, indacaterol; LS, least squares; PBO, placebo; Salb, salbutamol; S + F, salmeterol-fluticasone.

during this study. No patient discontinued from the study due to adverse events. Notably, high pulse rate (>90 beats per minute) and systolic blood pressure (>140 mmHg) were more frequently reported for patients taking placebo than for those taking indacaterol. No patient in the study had an absolute corrected QT (Fridericia's) value of >500 msec

or a change from baseline of 60 msec. Furthermore, no patient had newly occurring or worsening clinically notable values for serum potassium (minimum postbaseline value <3.0 mmol/L) during this study, and only three patients (one patient each who took indacaterol 150 and 300 µg and salmeterol-fluticasone 50/500 µg) had newly occurring or

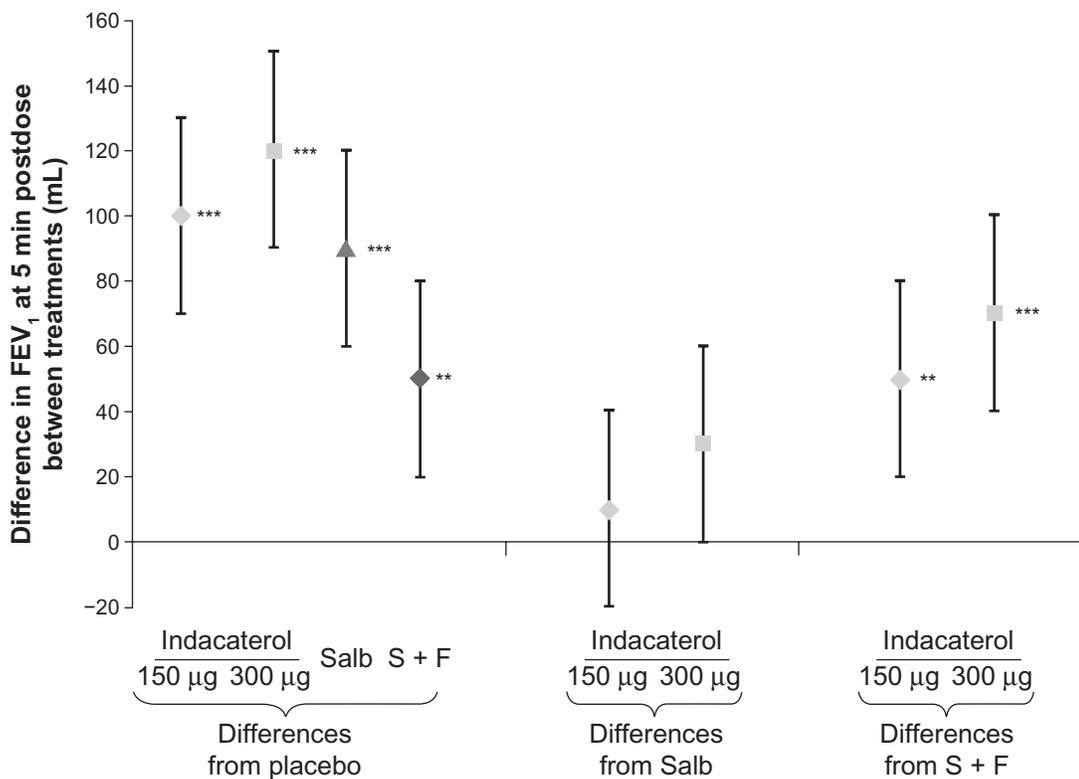


Figure 2 Least squares mean treatment differences (±95% confidence interval) in FEV₁ at five minutes postdose.

Note: Differences significant at ***P* < 0.01 and ****P* < 0.001.

Abbreviations: FEV₁, forced expiratory volume in one second; Salb, salbutamol; S + F, salmeterol-fluticasone.

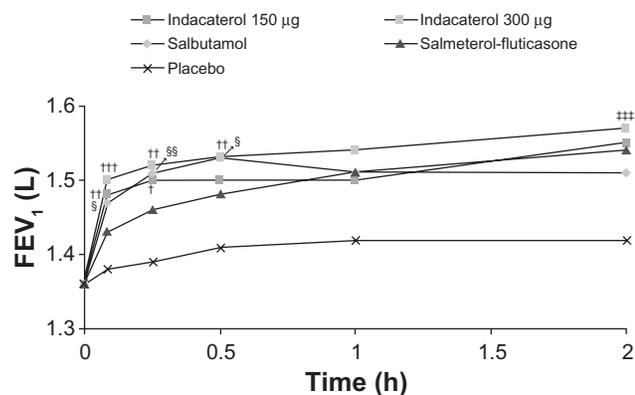


Figure 3 Serial least squares mean FEV₁ over two hours.

Notes: $P < 0.001$ for both indacaterol doses versus placebo at all time points; $P < 0.001$ for salbutamol versus placebo at all time points; $P < 0.01$ for salmeterol-fluticasone at all time points; † $P < 0.05$; †† $P < 0.01$; ††† $P < 0.001$ for indacaterol versus salmeterol-fluticasone; ††† $P < 0.001$ indacaterol versus salbutamol; § $P < 0.05$; §§ $P < 0.01$ for salbutamol versus salmeterol-fluticasone.

Abbreviations: FEV₁, forced expiratory volume in one second; h, hours.

worsening of clinically notable values for blood glucose (maximum postbaseline value >9.99 mmol/L).

Discussion

As with many chronic conditions, adherence to treatment is low in COPD, which is perhaps a reflection of the high

rate of comorbid conditions and consequent polypharmacy. Although indacaterol is being developed for maintenance treatment of COPD, and not as rescue medication, fast onset on the first dose may help patients perceive an immediate symptomatic benefit. This, together with the sustained 24-hour duration of bronchodilation¹⁴ and a good overall safety and tolerability profile,¹² which have been observed in other indacaterol clinical studies, may lead to improved patient adherence.¹⁵

This study was therefore designed to compare the onset of action of single doses of indacaterol 150 and 300 µg with salbutamol, salmeterol-fluticasone, and placebo. The study was conducted as planned, with 96.6% of randomized patients completing their assigned treatments. This study achieved all primary and secondary objectives. For the primary efficacy variable (FEV₁ at five minutes post-dose), both indacaterol doses were superior to placebo, with treatment–placebo differences of 100 and 120 mL for the 150 and 300 µg doses, respectively. Such differences (ie, ≥ 100 mL) have been described as ones that patients can perceive, and therefore can be considered clinically relevant.¹⁶ Furthermore, the bronchodilator efficacy of both indacaterol doses at this time point was similar to that

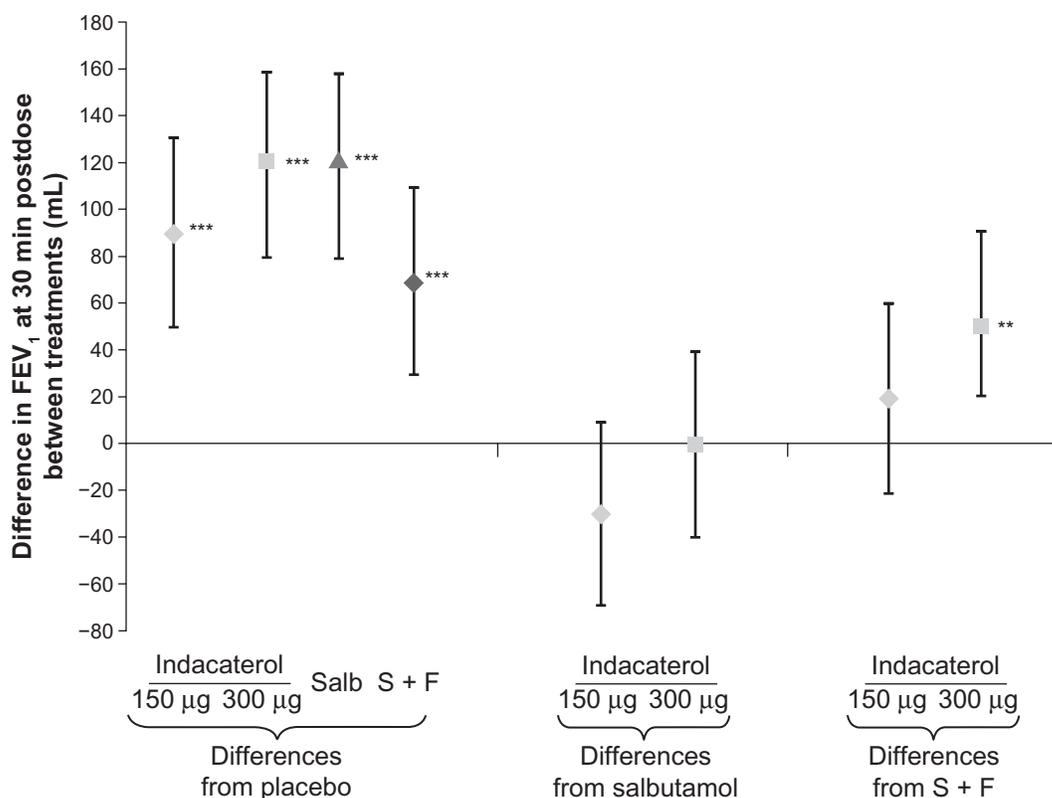


Figure 4 Least squares mean treatment differences ($\pm 95\%$ confidence interval) in FEV₁ at 30 minutes postdose.

Note: Differences significant at ** $P < 0.01$ and *** $P < 0.001$.

Abbreviations: FEV₁, forced expiratory volume in one second; Salb, salbutamol; S + F, salmeterol-fluticasone.

and Ben Kramer are employees of Novartis. Beatrix Balint and Henrik Watz have no actual or potential conflict of interest, including any financial relationships with industry (eg, employment, consultancies, stock ownership, honoraria, expert testimony), either directly or through immediate family.

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